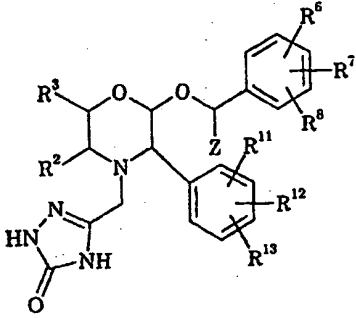


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 413/06, 249/02		A1	(11) International Publication Number: WO 99/65900
		(43) International Publication Date: 23 December 1999 (23.12.99)	
(21) International Application Number: PCT/GB99/01842 (22) International Filing Date: 10 June 1999 (10.06.99) (30) Priority Data: 9813025.5 16 June 1998 (16.06.98) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): COTTRELL, Ian, Frank [GB/GB]; M.S.D., Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). DOLLING, Ulf, H. [DE/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HANDS, David [GB/GB]; M.S.D., Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). WILSON, Robert, Darrin [GB/GB]; M.S.D., Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (74) Agent: HISCOCK, Ian, James; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: CHEMICAL SYNTHESIS OF MORPHOLINE DERIVATIVES			
 <p style="text-align: right;">(I)</p>			
(57) Abstract The present invention relates to a process for the preparation of morpholine derivatives of formula (I) which are useful as a therapeutic agents.			

FOR THE PURPOSES OF INFORMATION ONLY

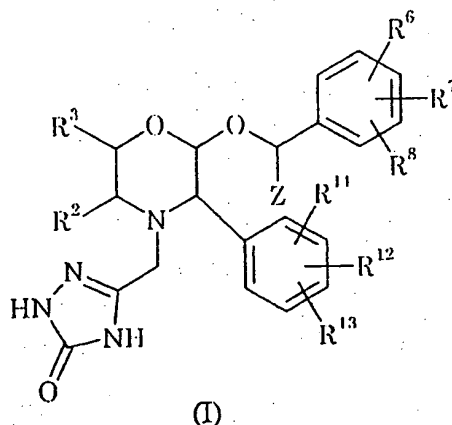
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

CHEMICAL SYNTHESIS OF MORPHOLINE DERIVATIVES

The present invention relates to a process for the preparation of morpholine derivatives, and in particular, the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, which are useful as therapeutic agents.

Compounds of formula (I), below, which are described in International patent specification No. WO 95/16679 (published 22nd June 1995), are potent and selective substance P (or neurokinin-1) receptor antagonists.



wherein

R^2 and R^3 are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) C_{2-6} alkenyl, and
- (4) phenyl;

R^6 , R^7 and R^8 are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) fluoro,
- (4) chloro,
- (5) bromo,

(6) iodo, and

(7) $-\text{CF}_3$;

R^{11} , R^{12} and R^{13} are independently selected from the group consisting of:

(1) hydrogen,

5 (2) C_{1-6} alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

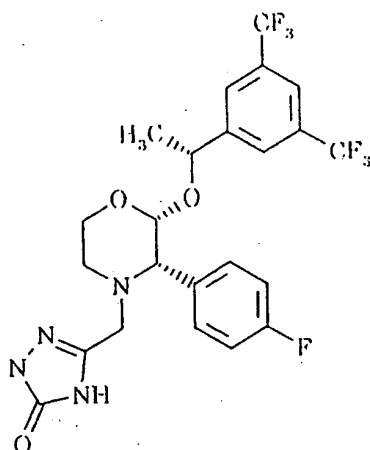
(6) iodo, and

10 (7) $-\text{CF}_3$; and

Z is C_{1-4} alkyl.

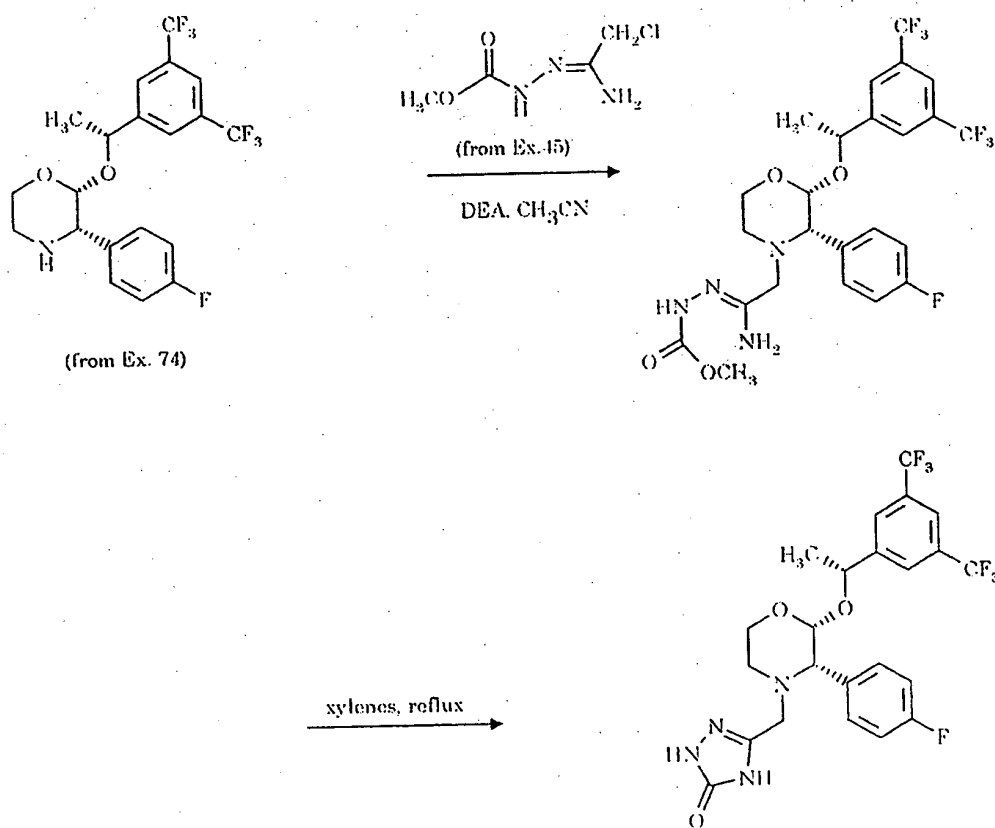
In particular, the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine has shown potential in the
15 treatment of emesis, depression and anxiety. Substance P antagonists are also being investigated for other neuropsychiatric diseases, including bipolar disorder and schizophrenia, as well as postherpetic neuralgia and pain.

International patent specification No. WO 95/16679 describes the
20 preparation of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine (hereinafter referred to as Compound A), which has the structure:



Compound A

by a two-step process starting from 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine. With reference to Examples 70 and 75 in WO 95/16679, Compound A is prepared as follows:

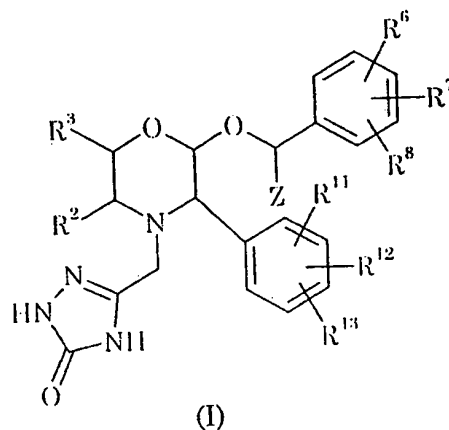


Compound A

This prior art process and in particular its requirement for a high temperature cyclisation step presents a number of practical difficulties which render it inconvenient when attempted on anything other than a relatively small scale. Therefore, there is a need for the development of a process which is readily amenable to scale-up and hence capable of practical application to the manufacturing plant.

The present invention accordingly provides a convenient, efficient process which utilizes a one-step alkylation with 3-chloromethyl-1,2,4-triazolin-5-one at ambient temperature that produces compounds of formula (I), and in particular Compound A, in a higher yield than the prior art two-step synthesis and which avoids a high temperature cyclisation. The novel process of the present invention is not only more energy efficient (since it requires no heating), but it is also more productive allowing for a shorter time-cycle on large scale and a higher operating concentration. The ability to effect the process of the present invention in one reaction vessel, in which the desired product crystallises from the reaction mixture at ambient temperature is a clear advantage over the prior art synthesis.

Thus, in a first aspect of the present invention, there is provided a process for the preparation of a compound of formula (I)



wherein

R² and R³ are independently selected from the group consisting of:

- (1) hydrogen,

- (2) C₁₋₆alkyl,
- (3) C₂₋₆alkenyl, and
- (4) phenyl;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of:

- 5 (1) hydrogen,
- (2) C₁₋₆alkyl,
- (3) fluoro,
- (4) chloro,
- (5) bromo,
- 10 (6) iodo, and
- (7) -CF₃;

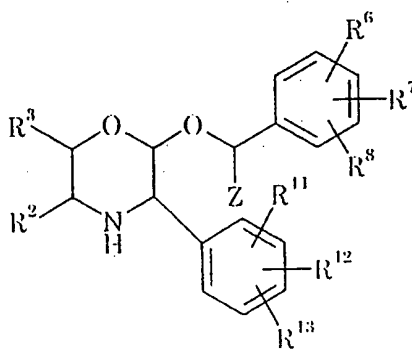
R¹¹, R¹² and R¹³ are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆alkyl,
- 15 (3) fluoro,
- (4) chloro,
- (5) bromo,
- (6) iodo, and
- (7) -CF₃; and

20 Z is C₁₋₆alkyl,

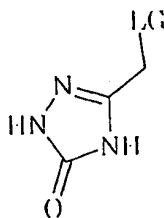
which comprises:

- (i) reacting a compound of formula (II)



(II)

or a salt thereof, wherein R^2 , R^3 , R^6 , R^7 , R^8 , R^{11} , R^{12} , R^{13} and Z are as previously defined, with a compound of formula (III)



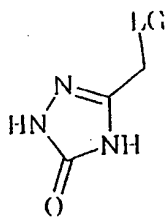
(III)

wherein LG is a leaving group selected from halogen (e.g. bromo, chloro or iodo) or an alkyl- or arylsulfonate group (e.g. mesylate or tosylate), in an organic solvent and in the presence of a base; and

(ii) collecting the resultant crystalline compound of formula (I).

In a particularly preferred aspect of the present invention, there is provided a process for the preparation of the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine which comprises:

(i) reacting 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine or a salt thereof, with a compound of formula (III)



(III)

15

as previously defined, in an organic solvent and in the presence of a base; and

(ii) collecting the resultant crystalline 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-

20

1H,4H-1,2,4-triazolo)methyl)morpholine.

In the compounds of formulae (I) and (II), preferably R^2 and R^3 are both independently hydrogen.

In the compounds of formulae (I) and (II), preferably R^6 and R^7 are independently selected from fluoro and $-CF_3$. In particular, R^6 and R^7 are
5 both independently $-CF_3$.

In the compounds of formulae (I) and (II), preferably R^8 is hydrogen.

In the compounds of formulae (I) and (II), preferably R^{11} is hydrogen or fluoro.

In the compounds of formulae (I) and (II), preferably R^{12} and R^{13} are
10 both independently hydrogen.

In the compounds of formulae (I) and (II), preferably Z is $-CH_3$.

In the compound of formula (III), preferably, the leaving group LG is chloro.

Suitable bases of use in the above reaction include organic bases or,
15 more preferably, inorganic bases. Suitable organic bases include diisopropylethylamine or triethylamine. Suitable inorganic bases include sodium hydride or potassium carbonate.

Suitable organic solvents of use in the above reaction include dimethylformamide (especially where an inorganic base is used) and
20 acetonitrile (especially where an organic base is used).

Most preferably, the above reaction is effected in dimethylformamide in the presence of potassium carbonate.

Conveniently, the above reaction is effected at room temperature.

Conveniently, the compound of formula (II), and in particular 2-(*R*)-
25 (1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-morpholine, of use in step (i) of the above reaction is in the form of its free base. Preferably the compound of formula (II), and in particular 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-morpholine, of use in step (i) of the above reaction is in the form of its (*R*)-
30 camphor sulfonic acid salt. More preferably, the compound of formula (II), and in particular 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-

(S)-(4-fluorophenyl)morpholine. of use in step (i) of the above reaction is in the form of its *para*-toluenesulfonic acid salt.

According to a further or alternative aspect of the present invention, there is provided a process for the preparation of 3-chloromethyl-1,2,4-triazolin-5-one which comprises:

- (i) treatment of semicarbazide hydrochloride with benzyloxyacetyl chloride under Schotten-Baumann conditions to give benzyloxyacetylsemicarbazide;
- (ii) cyclisation of the product of step (i) under basic conditions to give 3-benzyloxymethyl-1,2,4-triazolin-5-one;
- (iii) hydrogenation of the product of step (ii) to give 3-hydroxymethyl-1,2,4-triazolin-5-one; and
- (iv) treatment of the product of step (iii) with a chlorinating agent to give 3-chloromethyl-1,2,4-triazolin-5-one.

According to yet a further or alternative aspect of the present invention, there is provided a process for the preparation of 3-hydroxymethyl-1,2,4-triazol-5-one which comprises steps (i) to (iii) as described above.

In step (i) above, the Schotten-Baumann conditions preferably involve use of aqueous alkali in a suitable solvent such as an ether, for example, tetrahydrofuran, at a reduced temperature, for example, between -10°C and +10°C, preferably 0°C. A particularly suitable aqueous alkali is aqueous sodium hydroxide.

In step (ii) above, cyclisation is preferably effected in the presence of a base such as an alkali metal hydroxide, for example, sodium hydroxide, at an elevated temperature, conveniently at reflux.

In step (iii) above, hydrogenation may be effected by catalytic hydrogenation using hydrogen in a suitable organic solvent such as an alcohol, for example, methanol, in the presence of a noble metal catalyst such as palladium or platinum or an oxide thereof on a support such as charcoal, and conveniently at room temperature and pressure. More

preferably, the hydrogenation is effected by transfer hydrogenation in a suitable organic solvent such as an alcohol, for example, methanol, using a hydrogenation catalyst, in particular, palladium on charcoal, in the presence of a hydrogen donor such as sodium hypophosphite, triethylammonium formate, potassium formate, ammonium formate or cyclohexene. Ammonium formate in water is especially preferred. The transfer hydrogenation is preferably effected at an elevated temperature, for example, between 50°C and 70°C, and preferably between 55°C and 60°C.

In step (iv) above, the chlorinating agent is, for example, an inorganic acid chloride such as SOCl₂, PCl₅, PCl₃ and POCl₃. Thionyl chloride (SOCl₂) is particularly preferred. The reaction is preferably effected in an organic solvent such as acetonitrile, conveniently at room temperature and pressure.

The following non-limiting examples illustrate processes according to the present invention:

EXAMPLE 1

Preparation of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine

A solution of 3-chloromethyl-1,2,4-triazolin-5-one (3.18 g) in DMF (30 ml) was added over 1 hour to a slurry of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine (R)-camphor sulfonic acid salt (15 g) and potassium carbonate (7.71 g) in DMF (100 ml) at 22°C. The reaction mixture was aged at 22°C for 20 minutes, then water (400 ml) was added over 30 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (400 ml), air dried and dried *in vacuo* at 45-50°C. Yield = 11.4 g; 98.1% HPLC w/w assay; 93.2% assay yield; (97.1A% HPLC profile).

EXAMPLE 2

Steps (i) and (ii) Preparation of 3-benzyloxymethyl-1,2,4-triazolin-5-one

5 Sodium hydroxide pellets (10.83 g) were added to a cold (0°C), vigorously stirred, solution of semicarbazide hydrochloride (15.1 g) in water (10 ml)/THF (50 ml) under a nitrogen atmosphere. A solution of benzyloxyacetyl chloride (25 g) in THF (100 ml) was added over five minutes and the mixture aged at 0°C for 2 hours (reaction complete by
10 HPLC).

THF was removed under reduced pressure, 2M sodium hydroxide (60 ml) was added and the solution heated to reflux temperature for 5 hours. The reaction mixture was cooled to room temperature and left to stand for 18 hours. The solution was neutralised with 6M hydrochloric
15 acid and the slurry cooled in an ice-bath for 1 hour. The product was collected by filtration, washed with cold water (10 ml) and dried *in vacuo*. 3-Benzyloxy-methyl-1,2,4-triazolin-5-one (16.7 g) was obtained in 60% yield as a white crystalline solid. mp. 190-192°C; ¹H NMR in d₆ DMSO δ=4.20 (2H, s, PhCH₂), 4.42 (2H, s, OCH₂=N), 7.25 (5H, s, Ph), 11.34 (1H, s, NH) and 11.50 (1H, s, NH) ppm and ¹³C NMR in d₆ DMSO, δ=64.1
20 (OCH₂C=N), 72.4 (PhCH₂O), 128.5 (Ph), 128.6 (Ph), 129.1 (Ph), 138.5 (Ph), 145.4 (C=N) and 157.1 (NHCONH) ppm; mass spectroscopy M+H = 206, M+NH₄ = 223.

25 Step (iii) Preparation of 3-hydroxymethyl-1,2,4-triazolin-5-one

3-Benzyloxymethyl-1,2,4-triazolin-5-one (31g) and 10% palladium on charcoal (3.1 g) were slurried in methanol (200 ml), under a nitrogen atmosphere. A solution of ammonium formate (47.7 g) in water (20 ml) was added and the mixture was vigorously stirred and heated to 55-60°C.
30 10% Palladium on charcoal (3.1 g) was added after 2 hours and at 3 hours catalyst (1.55 g) and ammonium formate (9.5 g) in water (4 ml) were

charged. After 4 hours the reaction mixture was cooled to room temperature and left to stand overnight. The methanol solution was evaporated, under reduced pressure, to low volume and flushed by continuous addition of methanol (3L), at 50-55°C, to remove the excess ammonium formate. The hot mixture was filtered through solka floc (15 g), the filtrate concentrated to low volume and solvent switched to acetonitrile (2 x 400 ml). The slurry was concentrated to about 100 ml, the product collected by filtration and then dried *in vacuo*. 3-Hydroxymethyl-1,2,4-triazolin-5-one (17.1 g) was obtained in 98.3% yield mp. 187-189°C (Lit = 187°C); ¹H NMR in d₆ DMSO δ= 4.34 (2H, s, HOCH₂) and 11.42 (2H, bs NH) ppm and ¹³C NMR in d₆ DMSO δ=56.3 (HOCH₂), 148.5 (CH₂C=N) and 157.1 (NHCONH) ppm; mass spectroscopy M+H=116, M+NH₄=133.

EXAMPLE 3

15

Preparation of 3-Chloromethyl-1,2,4-triazolin-5-one

Thionyl chloride (19.9 g) was added, over five minutes, to a slurry of 3-hydroxymethyl-1,2,4-triazolin-5-one (17 g) in acetonitrile (170 ml) at 20°C under a nitrogen atmosphere. The reaction mixture was aged at 20°C for 18 hours. [Note: after 30 minutes all the starting material had dissolved. At 1 hour the product began to crystallise]. TLC analysis (SiO₂; ethyl acetate/methanol (9/1); I₂) indicated that the reaction was complete. Hexane (510 ml) was added in one portion, the reaction cooled in an ice bath for 1 hour and the product collected by filtration. The solid was washed with hexane (100 ml) and dried *in vacuo*. 3-Chloromethyl-1,2,4-triazolin-5-one (17.2 g) was obtained as a white solid in 87.4% yield. mp 197-199°C; ¹H NMR in d₆ DMSO δ= 4.43 (2H, s, CH₂), 11.48 (1H, s, NH) and 11.64 (1H, s, NH) ppm and ¹³C NMR in d₆ DMSO, δ=37.0 (ClCH₂), 144.4 (CH₂C=N) and 156.8 (NHCONH) ppm.

30

EXAMPLE 4

Alternative Preparation of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine

(1) Alternative Method using N,N-diisopropylethylamine/DMF

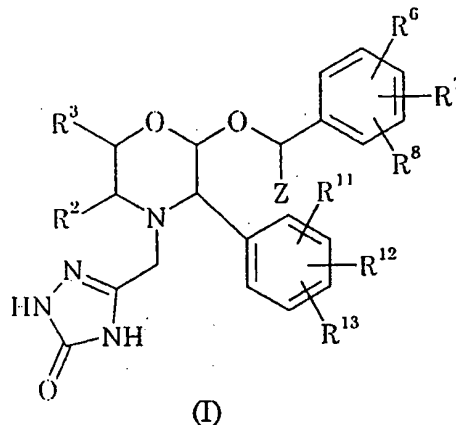
A solution of 3-chloromethyl-1,2,4-triazolin-5-one (2.56 g) in DMF (20 ml) was added over 1 hour to a slurry of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine *para*-toluenesulfonic acid salt (12 g) and N,N-diisopropylethylamine (5.15 g) in DMF (40 ml) at 21°C. The reaction was aged at 21-23°C for 30 minutes, then water (120 ml) was added over 20 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (96 ml), air dried and dried *in vacuo* at 50°C. Yield = 9.65 g; 99.7% isolated yield.

(2) Alternative Method using potassium carbonate/DMF

A solution of 3-chloromethyl-1,2,4-triazolin-5-one (1.40 g) in DMF (13.5 ml) was added over 1 hour to a slurry of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine *para*-toluenesulfonic acid salt (6.77 g) and potassium carbonate (1.55 g) in DMF (27 ml) at 19°C. The reaction was aged at 19-21°C for 30 minutes, then water (81 ml) was added over 20 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (54 ml), air dried and dried *in vacuo* at 50°C. Yield = 5.37 g; 98.0% HPLC w/w assay; 96.4% assay yield.

CLAIMS:

1. A process for the preparation of a compound of formula (I)



5 wherein

R^2 and R^3 are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) C_{2-6} alkenyl, and
- 10 (4) phenyl;

R^6 , R^7 and R^8 are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) fluoro,
- 15 (4) chloro,
- (5) bromo,
- (6) iodo, and
- (7) $-CF_3$;

R^{11} , R^{12} and R^{13} are independently selected from the group consisting of:

- 20 (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) fluoro,
- (4) chloro,
- (5) bromo,

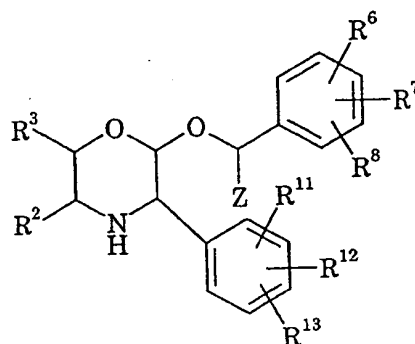
(6) iodo, and

(7) $-\text{CF}_3$; and

Z is C_{1-4} alkyl,

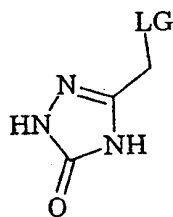
which comprises:

- 5 (i) reacting a compound of formula (II)



(II)

or a salt thereof, wherein R^2 , R^3 , R^6 , R^7 , R^8 , R^{11} , R^{12} , R^{13} and Z are as previously defined, with a compound of formula (III)

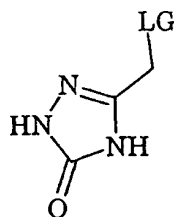


(III)

- 10 wherein LG is a leaving group selected from halogen (e.g. bromo, chloro or iodo) or an alkyl- or arylsulfonate group (e.g. mesylate or tosylate), in an organic solvent and in the presence of a base; and
- (ii) collecting the resultant crystalline compound of formula (I).

- 15 2. A process for the preparation of the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine which comprises:

(i) reacting 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine or a salt thereof, with a compound of formula (III)



(III)

5 as defined in Claim 1, in an organic solvent and in the presence of a base;
and

(ii) collecting the resultant crystalline 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine.

10

3. A process according to Claim 1 or Claim 2 wherein the leaving group LG is chloro.

4. A process according to Claim 1 or Claim 2 wherein the base is
15 an organic base.

5. A process according to Claim 4 wherein the organic base is selected from diisopropylethylamine or triethylamine.

20

6. A process according to Claim 1 or Claim 2 wherein the base is an inorganic base.

7. A process according to Claim 6 wherein the inorganic base is selected from sodium hydride or potassium carbonate.

25

8. A process according to any one of Claims 1 to 5 wherein the organic solvent is acetonitrile.

9. A process according to any one of Claims 1 to 3, 6 or 7
5 wherein the organic solvent is dimethylformamide.

10. A process according to Claim 1 or Claim 2 wherein step (i) is effected in dimethylformamide in the presence of potassium carbonate.

10 11. A process according to any one of Claims 1 to 10 wherein the reaction is effected at room temperature.

12. A process according to any one of Claims 2 to 11 wherein the 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-
15 fluorophenyl)morpholine of use in step (i) is in the form of its free base or its (*R*)-camphor sulfonic acid salt or its *para*-toluenesulfonic acid salt.

13. A process for the preparation of 3-chloromethyl-1,2,4-triazolin-5-one which comprises:

- 20 (i) treatment of semicarbazide hydrochloride with benzyloxyacetyl chloride under Schotten-Baumann conditions to give benzyloxyacetylsemicarbazide;
- (ii) cyclisation of the product of step (i) under basic conditions to give 3-benzyloxymethyl-1,2,4-triazolin-5-one;
- 25 (iii) hydrogenation of the product of step (ii) to give 3-hydroxymethyl-1,2,4-triazolin-5-one; and
- (iv) treatment of the product of step (iii) with a chlorinating agent to give 3-chloromethyl-1,2,4-triazolin-5-one.

30 14. A process for the preparation of 3-hydroxymethyl-1,2,4-triazol-5-one which comprises

(i) treatment of semicarbazide hydrochloride with benzyloxyacetyl chloride under Schotten-Baumann conditions to give benzyloxyacetylsemicarbazide;

(ii) cyclisation of the product of step (i) under basic conditions to give 3-benzyloxymethyl-1,2,4-triazolin-5-one; and

(iii) hydrogenation of the product of step (ii) to give 3-hydroxymethyl-1,2,4-triazolin-5-one.

15. A process according to Claim 13 or 14 wherein, in step (i), the Schotten-Baumann conditions involve use of aqueous alkali in an ether, at a reduced temperature.

16. A process according to Claim 15 wherein the aqueous alkali is aqueous sodium hydroxide.

17. A process according to Claim 15 or 16 wherein the ether is tetrahydrofuran.

18. A process according to any one of Claims 15 to 17 wherein the Schotten Baumann reaction is effected between -10°C and $+10^{\circ}\text{C}$.

19. A process according to Claim 13 or 14 wherein, in step (ii), cyclisation is effected in the presence of a base at an elevated temperature.

20. A process according to Claim 19 wherein the base is an alkali metal hydroxide.

21. A process according to Claim 20 wherein the alkali metal hydroxide is sodium hydroxide.

22. A process according to any one of Claims 19 to 21 wherein the reaction is effected at reflux.

5 23. A process according to Claim 13 or 14 wherein, in step (iii), hydrogenation is effected by catalytic hydrogenation using hydrogen in an organic solvent, and in the presence of a noble metal catalyst on a support.

24. A process according to Claim 23 wherein the organic solvent is an alcohol.

10

25. A process according to Claim 24 wherein the alcohol is methanol.

15 26. A process according to any one of Claims 23 to 25 wherein the noble metal catalyst is palladium or platinum or an oxide thereof.

27. A process according to any one of Claims 23 to 26 wherein the support is charcoal.

20

28. A process according to any one of Claims 23 to 27 wherein the reaction is effected at room temperature and pressure.

25 29. A process according to Claim 13 or 14 wherein, in step (iii), hydrogenation is effected by transfer hydrogenation in a organic solvent using a hydrogenation catalyst in the presence of a hydrogen donor.

30. A process according to Claim 29 wherein the organic solvent is an alcohol.

30

31. A process according to Claim 30 wherein the alcohol is methanol.

32. A process according to any one of Claims 29 to 31 wherein the hydrogenation catalyst is palladium on charcoal.

5 33. A process according to any one of Claims 29 to 32 wherein the hydrogen donor is selected from sodium hypophosphite, triethylammonium formate, potassium formate, ammonium formate and cyclohexene.

10 34. A process according to Claim 33 wherein the hydrogen donor is ammonium formate in water.

35. A process according to any one of Claims 29 to 34 wherein the transfer hydrogenation is effected at an elevated temperature.

15 36. A process according to Claim 35 wherein the reaction is effected at a temperature between 50°C and 70°C.

20 37. A process according to Claim 13 wherein, in step (iv), the chlorinating agent is an inorganic acid chloride.

38. A process according to Claim 37 wherein the inorganic acid chloride is selected from SOCl_2 , PCl_5 , PCl_3 and POCl_3 .

25 39. A process according to Claims 37 or 38 wherein the reaction is preferably effected in an organic solvent.

40. A process according to Claim 39 wherein the organic solvent is acetonitrile.

30 41. A process according to any one of Claims 37 to 40 wherein the reaction is effected at room temperature and pressure.

INTERNATIONAL SEARCH REPORT

International Application No

PC./GB 99/01842

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/06 C07D249/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 30674 A (MERCK SHARP & DOHME ;HAWORTH KAREN ELIZABETH (GB); TEALL MARTIN RI) 16 November 1995 (1995-11-16) page 19 - page 20; claims; example 2	1-41
Y	WO 95 23798 A (DORN CONRAD P ;HALE JEFFREY J (US); MACCOSS MALCOLM (US); MERCK &) 8 September 1995 (1995-09-08) page 94; claims	1-41
Y	WO 95 18124 A (MERCK SHARP & DOHME ;BAKER RAYMOND (GB); HARRISON TIMOTHY (GB); MA) 6 July 1995 (1995-07-06) page 36 - page 43; claims	1-41
	--- -/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 August 1999

Date of mailing of the international search report

17/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

International Application No.

PC 99/01842

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 16679 A (LADDUWAHETTY TAMARA ; WILLIAMS BRIAN JOHN (GB); CHAMBERS MARK STUAR) 22 June 1995 (1995-06-22) cited in the application page 112 - page 122; claims	1-41
Y	CHEMICAL ABSTRACTS, vol. 76, no. 7, 1972 Columbus, Ohio, US; abstract no. 34220, ARTEMOV V.N. ET AL.: "Formation and recyclization of heterocycles" XP002113533 abstract & KHIM.-FARM. ZH., vol. 5, no. 11, 1971, pages 6-10,	13-41
Y	CHEMICAL ABSTRACTS, vol. 71, no. 13, 1969 Columbus, Ohio, US; abstract no. 70540, SHVAIKA O.P. ET AL.: "Recyclization of azolidones under the influence of hydrazine" XP002113534 abstract & DOKL. AKAD. NAUK SSSR, vol. 186, no. 5, 1969, pages 1102-1105,	13-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application no.

PLI/GB 99/01842

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9530674 A	16-11-1995	AU 690682 B	30-04-1998
		AU 2349395 A	29-11-1995
		CA 2189141 A	16-11-1995
		EP 0758329 A	19-02-1997
		JP 10500944 T	27-01-1998
		US 5747491 A	05-05-1998
WO 9523798 A	08-09-1995	AU 700611 B	07-01-1999
		AU 1975095 A	18-09-1995
		BG 100798 A	31-03-1997
		BR 9507046 A	09-09-1997
		CA 2183250 A	08-09-1995
		CN 1147254 A	09-04-1997
		CZ 9602588 A	12-03-1997
		EP 0748320 A	18-12-1996
		FI 963450 A	03-09-1996
		HR 950099 A	30-04-1998
		HU 76324 A	28-08-1997
		JP 9509935 T	07-10-1997
		LV 11688 A	20-02-1997
		LV 11688 B	20-06-1997
		NO 963675 A	04-11-1996
		NZ 282586 A	28-07-1998
		PL 316143 A	23-12-1996
		SK 112396 A	05-03-1997
		US 5716942 A	10-02-1998
		US 5512570 A	30-04-1996
		US 5691336 A	25-11-1997
		US 5780467 A	14-07-1998
		ZA 9501780 A	15-11-1995
WO 9518124 A	06-07-1995	AU 685209 B	15-01-1998
		AU 1322395 A	17-07-1995
		BG 100644 A	31-03-1997
		BR 9408442 A	05-08-1997
		CA 2178219 A	06-07-1995
		CN 1139927 A	08-01-1997
		CZ 9601898 A	11-12-1996
		EP 0737192 A	16-10-1996
		HU 75872 A	28-05-1997
		JP 9507484 T	29-07-1997
		LV 11687 A	20-02-1997
		LV 11687 B	20-10-1997
		NO 962749 A	28-08-1996
		NZ 277839 A	26-01-1998
		PL 315182 A	14-10-1996
		SG 52217 A	28-09-1998
		SK 83996 A	06-11-1996
		US 5612337 A	18-03-1997
		ZA 9410317 A	10-10-1995
		FI 951762 A	13-10-1995
		HR 950222 A	31-08-1997
WO 9516679 A	22-06-1995	AU 701862 B	04-02-1999
		AU 1437595 A	03-07-1995
		BG 100715 A	31-01-1997
		BR 9408351 A	26-08-1997
		CA 2178949 A	22-06-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01842

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9516679 A		CN 1142819 A	12-02-1997
		CZ 9601772 A	11-12-1996
		EP 0734381 A	02-10-1996
		FI 962489 A	13-08-1996
		HR 941000 A	30-06-1997
		HU 76476 A	29-09-1997
		JP 9506628 T	30-06-1997
		LV 11617 A	20-12-1996
		LV 11617 B	20-04-1997
		NO 962523 A	16-08-1996
		NZ 278222 A	27-05-1998
		PL 315153 A	14-10-1996
		SK 75396 A	04-12-1996
		US 5637699 A	10-06-1997
		US 5719147 A	17-02-1998
		US 5872116 A	16-02-1999
		US 5922706 A	13-07-1999
		ZA 9410008 A	15-07-1996